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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/335,218	06/17/99	WRIGHT	D P-4423

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EXAMINER	
FORMAN, B	
ART UNIT	**PAPER NUMBER**
1655	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/335,218	Applicant(s) WRIGHT ET AL.	
	Examiner BJ Forman	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *25-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24 and 55-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *13* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The request filed on 17 June 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/335,218 is acceptable and a CPA has been established. An action on the CPA follows.

2. This action is in response to papers filed 20 June 2001 in Paper No. 16 in which Applicants Responded to the Office Action of Paper No.12, dated 26 February 2001. The previous rejections in the Office Action of Paper No. 12 withdrawn in view of Applicant's arguments and new grounds for rejection. Applicant's arguments regarding the previous rejections have been considered, but are mooted in view of the withdrawn rejections and new grounds for rejection. New grounds for rejection are discussed.

Currently claims 1-24 55-62 are under prosecution.

Claim Objections

3. Claim 55, is objected to because "the" is misspelled in line 1 of step c).

Appropriate correction is required.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-5, 7-19, 24, 55-57, 59 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Walker et al. (Nucleic Acids Research, 1992, 20(7): 1691-1696).

Regarding Claim 1, Newton et al. disclose a method for detecting a single nucleotide polymorphism in a target comprising: hybridizing a detector primer to the target, wherein the detector primer comprises a diagnostic nucleotide for the single nucleotide polymorphism which is a 3' terminal nucleotide of the detector primer (Column 4, lines 31-67); determining efficiency of the detector primer extension; and detecting the presence or absence of the single nucleotide polymorphism based on the efficiency of the detector primer extension (Column 13, lines 11-34) wherein the amplification reaction is an isothermal reaction (Column 7, lines 50-60) but they do not teach the method comprising a second primer such that extension of the second primer displaces the detector primer. However, second primers which upon extension displace a detector primer (i.e. Strand Displacement Amplification (SDA)) was well known in the art at the time the claimed invention was made as taught by Walker et al. Specifically, Walker et al. teach a method similar to that of Newton et al. for detecting a target comprising: hybridizing a detector primer and a second primer to the target such that extension of the second primer displaces the detector primer, displacing the detector primer from the target by extension of an upstream primer and amplifying the target (page 1692, Fig. 1) wherein displacement by extension of the second primer generates target sequence of defined 3' and 5' ends with increased efficiency and decreased non-specific primer binding (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the detector primer extension of Newton et al. by also extending an upstream primer to displace the detector primer for the expected benefits of increased efficiency and decreased non-specific product formation as taught by Walker et al. (Abstract) to thereby efficiently and accurately detect a single nucleotide polymorphism.

Regarding Claim 2, Newton et al. teach the method wherein the single nucleotide polymorphism is identified using the detector primer i.e. the primer is extended only when the terminal nucleotide of the primer is complementary to the target (Column 12, lines 47-59).

Regarding Claim 3, Newton et al. teach the method wherein the single nucleotide polymorphism is identified using multiple detector primers comprising different diagnostic nucleotides (Column 30, Example 1).

Regarding Claim 4, Newton et al. teach the method wherein two detector primers are used to identify which of two possible alleles is present in the target sequence (Column 30, Example 1).

Regarding Claim 5, Newton et al. teach the method wherein four detector primers are used to identify the nucleotide present in the target sequence at the position of the single nucleotide polymorphism (Column 32, Example 4).

Regarding Claim 7, Newton et al. teach the method wherein the detector primer further comprises a nucleotide which forms a nondiagnostic mismatch with the target sequence (Column 12, lines 22-26).

Regarding Claim 8, Newton et al. teach the method wherein the nondiagnostic nucleotide is positioned within fifteen nucleotides of the diagnostic nucleotide in the detector primer (Column 12, lines 27-32).

Regarding Claim 9, Newton et al. teach the method wherein the nondiagnostic nucleotide is positioned 1-5 nucleotides from the diagnostic nucleotide in the detector primer (Column 12, lines 27-32).

Regarding Claim 10, Newton et al. teach the method wherein the nondiagnostic nucleotide is adjacent to the diagnostic nucleotide in the detector primer i.e. 1, 2 or 3 bases from the terminal nucleotide (Column 12, lines 27-32).

Regarding Claim 11, Newton et al. teach the method wherein the detector primer is about 15-36 nucleotides long (Column 11, lines 12-20).

Regarding Claim 12, Newton et al. teach the method wherein the detector primer is about 18-24 nucleotides long (Column 11, lines 12-20).

Regarding Claim 13, Newton et al. do not teach the method comprising a second primer. However, Walker et al. teach the similar method wherein the second primer is an amplification primer for use in an amplification reaction (page 1692, left column first full paragraph and Fig. 1). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the single primer amplification of Newton et al. by also using a second upstream amplification primer for the expected benefit of enhanced amplification of single-stranded or double-stranded targets as taught by Walker et al. (page 1695, left column, last paragraph-right column first paragraph).

Regarding Claim 14, Newton et al. teach the method is an isothermal amplification reaction (Column 7, lines 50-60) but they do not teach the reaction is selected from SDA, 3SR, NASBA and TMA. However, Walker et al. teach the similar method wherein the reaction is SDA (Abstract) wherein the SDA method eliminates temperature cycling, permits amplification under high stringency conditions and amplifies low-abundance targets (page 1695, right column last full paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the isothermal amplification method of Newton et al. with the SDA method of Walker et al. for the expected benefits of SDA taught by Walker et al. i.e. permits amplification under high stringency conditions and amplifies low-abundance targets (page 1695, right column last full paragraph) to thereby specifically amplify a rare single nucleotide polymorphism.

Regarding Claim 15, Newton et al. teach the method wherein the detector primer is about 12-50 nucleotides long (Column 11, lines 12-20).

Regarding Claim 16, Newton et al. teach the method wherein the detector primer is about 12-24 nucleotides long (Column 11, lines 12-20).

Regarding Claim 17, Newton et al. teach the method wherein the detector primer is about 12-19 nucleotides long (Column 11, lines 12-20).

Regarding Claim 18, Newton et al. teach the method wherein the presence or absence of the single nucleotide polymorphism is detected by means of a label associated with the detector primer (Column 14, lines 40-48).

Regarding Claim 19, Newton et al. teach the method wherein the label becomes detectable upon extension of the detector primer (Column 8, lines 13-23).

Regarding Claim 24, Newton et al. teach the method wherein the efficiency of detector primer extension is determined quantitatively i.e. detection of heterozygous or homozygous samples (Column 13, lines 35-41).

Regarding Claim 55, Newton et al. teach a method for detecting a single nucleotide polymorphism in a target sequence comprising: hybridizing to the target sequence a detector primer comprising a diagnostic nucleotide for the single nucleotide polymorphism which is a 3' terminal nucleotide of the detector primer (Column 4, lines 31-58); extending the primer; and detecting the presence or absence of the single nucleotide polymorphism based on an efficiency of detector primer extension (Column 13, lines 11-34) but they do not teach the detector primer is displaced by extension of a second primer hybridized to the target sequence upstream of the detector primer. However, second primers which upon extension displace a detector primer (i.e. Strand Displacement Amplification (SDA)) was well known in the art at the time the claimed invention was made as taught by Walker et al. Specifically, Walker et al. teach a method similar to that of Newton et al. for detecting a target comprising: hybridizing a detector primer and a second primer to the target such that extension of the second primer displace the detector primer, displacing the detector primer from the target by extension of an upstream primer and amplifying the target (page 1692, Fig. 1) wherein displacement by extension of the second primer generates target sequence of defined 3' and 5' ends with increased efficiency and decreased non-specific primer binding (Abstract). It would have been obvious to one of

ordinary skill in the art at the time the claimed invention was made to modify the detector primer extension of Newton et al. by also extending an upstream primer to displace the detector primer for the expected benefits of increased efficiency and decreased non-specific product formation as taught by Walker et al. (Abstract) to thereby efficiently and accurately detect a single nucleotide polymorphism.

Regarding Claim 56, Newton et al. teach the method wherein the single nucleotide polymorphism is identified using the detector primer i.e. the primer is extended only when the terminal nucleotide of the primer is complementary to the target (Column 12, lines 47-59).

Regarding Claim 57, Newton et al. teach the method wherein the single nucleotide polymorphism is identified using multiple detector primers comprising different diagnostic nucleotides (Column 30, Example 1).

Regarding Claim 59, Newton et al. do not teach the method comprising a second primer. However, Walker et al. teach the similar method wherein the second primer is an amplification primer for use in an amplification reaction (page 1692, left column first full paragraph and Fig. 1). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the single primer amplification of Newton et al. by also using a second upstream amplification primer for the expected benefit of enhanced amplification of single-stranded or double-stranded targets as taught by Walker et al. (page 1695, left column, last paragraph-right column first paragraph).

Regarding Claim 62, Newton et al. teach the method wherein the diagnostic nucleotide is a 3' terminal nucleotide (Column 4, lines 31-67).

6. Claims 6 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Walker et al. (Nucleic Acids Research, 1992, 20(7): 1691-1696) as applied to Claims 1 and 55 respectively above and

further in view of Reynolds et al. (U.S. Patent No. 5,763,184, issued 9 June 1998) and Mullis et al. (U.S. Patent No. 4,683,195, issued 28 July 1987).

Regarding Claims 6 and 58, Newton et al. teach the method wherein the detector primer has a 5' tail sequence (Column 11, lines 40-45) and Walker et al. teach the similar method wherein the detector primer has a 5' tail sequence (page 1693, left column last paragraph) but Newton et al. and Walker et al. do not teach each of the multiple primers has a different 5' sequence. Reynolds et al. teach a similar method for detecting a single polynucleotide polymorphism comprising a detector primer wherein the detector primer has a 5' tail sequence and wherein the 5' tail sequence facilitates cloning and sequencing as taught by Mullis et al. (Column 11, lines 21-27) and Mullis et al. teach multiple primers comprise a different 5' tail sequence to facilitate cloning and sequencing of individual amplified products (Column 15, lines 38-47). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 5' tail sequence of the detector primers taught by Newton et al., Walker et al. and Reynolds to provide each detector primer with a different 5' tail sequence for the expected benefit of facilitating cloning and sequencing of individual amplified products as taught by Mullis et al. (Column 15, lines 38-47) to thereby simplify identification of individual single nucleotide polymorphic loci.

7. Claims 20, 21, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Walker et al. (Nucleic Acids Research, 1992, 20(7): 1691-1696) as applied to Claim 1 above and further in view of Chen et al. (Nucleic Acids Research, 1997, 25(2): 347-353).

Regarding Claims 20, 21, 60 and 61, Newton et al. teach the method wherein the presence or absence of the single nucleotide polymorphism is detected by means of a label

associated with the detector primer, wherein the label becomes detectable upon extension of the detector primer (Column 8, lines 13-23) but they do not teach the label is a fluorescent donor/quencher dye pair (Claims 20 and 60) and they do not teach a change in fluorescence is detected as an indication of the presence of the single nucleotide polymorphism (Claims 21 and 61). However, Chen et al. teach a similar method for detecting a single nucleotide polymorphism comprising hybridizing a detector primer to the target; amplifying the target by extension of the detector primer; and detecting the single nucleotide polymorphism and wherein the single nucleotide polymorphism is detected by a label associated with the detector primer, wherein the label produces a change in signal upon extension of the detector primer and wherein the label is a fluorescent donor/quencher pair and a decrease in donor dye (page 348, right column, first and second full paragraphs). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the fluorescence donor/quencher dye pair of Chen et al. wherein a change in fluorescence determines the presence of the single nucleotide polymorphism to the fluorescence detection of single nucleotide polymorphism of Newton et al. for the expected benefits of highly sensitive and specific detection of primer extension product as taught by Chen et al. (page 348. right column, second full paragraph).

8. Claims 22 & 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Walker et al. (Nucleic Acids Research, 1992, 20(7): 1691-1696) as applied to claim 1 above, and further in view of Thomas et al. (U.S. Patent No. 6,025,130, filed 23 May 1996). Newton et al. teach the method wherein a single nucleotide difference is detected in a target sequence but they do not teach a single nucleotide difference in the HFE gene is detected. However, the HFE i.e. Hereditary Hemochromatosis gene (HH) was known to have a single nucleotide difference in exon 4 as

taught by Thomas et al. (Column 11, lines 56-59 and Column 16, lines 59-65). Thomas et al. teach a single nucleotide difference i.e. mutation in exon 4 of the HH gene i.e. 24d1 (Column 16, lines 25-33) wherein the difference is responsible for the majority of hereditary hemochromatosis (Column 11, lines 63-64) and they teach primers for target-specific detection of the 24d1 difference (Column 17, lines 1-4 Fig 6A). Therefore, it would have been obvious to one of ordinary skill in the art to apply the target-specific detection of Newton et al. and Walker et al. to the HFE-specific primer and target sequences taught by Thomas et al. for the expected benefit of efficient gene-based diagnosis of disease-causing mutation i.e. known mutations in the HFE gene.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
July 11, 2001

S. Ziomer